NALOXONE KITS AND NALOXONE AUTOINJECTORS

Recommendations for Issuing Naloxone Kits and Naloxone Autoinjectors for the VA Overdose Education and Naloxone Distribution (OEND) Program

October 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives
in collaboration with the VA OEND National Support and Development Work Group

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. Local adjudication should be used until updated guidance and/or CFU are developed by the National PBM. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing.

The drug Product Information should be consulted for detailed prescribing information. Also see Naloxone Autoinjector Abbreviated Review at www.pbm.va.gov .

The **VA Overdose Education and Naloxone Distribution (OEND) program** is a harm reduction and risk mitigation initiative that aims to decrease opioid-related overdose deaths among VA patients The issuance of naloxone kits or autoinjectors constitutes just one component of the OEND program; opioid overdose prevention, recognition of opioid overdose and rescue response comprise other key components. While anyone may be educated and trained in these aspects of opioid overdoses, naloxone remains a medication obtainable only by prescription in most states in the U.S. Naloxone kit and autoinjector utilization and rates of opioid overdose and mortality will be tracked nationally in VA to evaluate the OEND program's performance. The PBM, MAP, and VPEs, in collaboration with the VA OEND National Support and Development Work Group, prepared the following recommendations to provide standardized guidance on the issuance of naloxone kits and autoinjectors under the VA OEND program.

CLINICAL RECOMMENDATIONS FOR OFFERING NALOXONE KITS AND NALOXONE AUTOINJECTORS

A prescription is required for naloxone kits and naloxone autoinjectors.

Discuss naloxone as an opioid harm reduction / risk mitigation option with patient and/or family/carer and document the discussion in the patient's medical records.

Offer naloxone kits to Veterans prescribed or using opioids who are at increased risk for opioid overdose or whose provider deems, based on their clinical judgment, that the Veteran has an indication for a naloxone kit. See examples of candidates for naloxone kits below.

Offer naloxone autoinjectors to those who are candidates for naloxone kits AND are unable to demonstrate assembly and administration of the IM and IN 'kit' naloxone in a timely manner.

Examples of Candidates for Naloxone Kits include but are not limited to Veterans with the following:

- Opioid use disorder diagnosis
- Prescription opioid misuse
- Injection opioid use
- Likely to have an opioid overdose such as individuals who receive VA or non-VA care in these situations:
  - Medication Assisted Treatment Program for opioid use disorder
  - Inpatient withdrawal management for opioid use disorder (particularly patients recently discharged from abstinence program)
  - HIV education / prevention program (which may provide care to injection opioid users)
  - Syringe access program
  - Outpatient and residential opioid use disorder treatment programs
  - Community meetings / Support group programs for opioid use disorder
  - Emergency departments (e.g., for opioid poisoning / overdose or intoxication)
  - Domiciliary care or community-based treatment for homeless Veterans
  - Primary health care (e.g., for follow-up of recent opioid poisoning / overdose or intoxication)

Also refer to Figure 1 **on page 5 as a guide for evidence-based classification of OEND candidates.** Table 2: o**n page 6 provides relative risks of opioid overdose deaths among Veterans prescribed opioids.**

Nonveterans requesting naloxone should be directed to community-based OEND programs. A national locator is available at http://hopeandrecovery.org/locations/ .

Individuals in hospice / palliative care are likely NOT appropriate candidates for naloxone kits or autoinjectors. OEND should be considered on a case by case basis and not routinely in hospice / palliative care patients.

Assessment Tools for Risk of Opioid-related Serious Toxicity or Overdose

- There are no published or fully validated tools available at this time that may be used to estimate patient risk for serious toxicity or overdose related to opioids.
- The manufacturer of naloxone autoinjector, Kaléo, is developing a tool that intends to estimate the probability of serious toxicity or overdose based on an index score based on the presence of various risk factors in patients prescribed opioids. The investigators identified the risk factors and retrospectively validated the tool using VHA administrative data.[1]
- Guideline-concordant risk assessment tools for predicting opioid aberrant drug-related behavior or problematic substance use should be used as part of a comprehensive risk assessment of patients being treated for substance use disorders or chronic pain. These tools have not been shown to be useful for predicting opioid overdose; however, they may provide information that is important to consider in the overall risk assessment and management of the patient.

Educate and train the patient on the proper use, storage, administration and disposal of naloxone kits and needles and autoinjectors.

- Explain that naloxone combined with overdose education complement, but do not replace, safe and responsible opioid use.
- Emphasize the importance of being familiar with naloxone administration technique before an emergency arises.
- Advise the patient about the importance of friends, family members, partners, and carers being educated and trained on the proper use, potential harms and limitations of naloxone treatment. A list of resources for education and training is included in the naloxone kits. Patient education resources include the following:
  - SAMHSA Opioid Overdose Prevention Toolkit: Contains safety advice for patients and resources for family members. http://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/SMA13-4742
  - Community-Based Overdose Prevention and Naloxone Distribution Program Locator: Identifies programs outside of the VA that distribute naloxone. http://hopeandrecovery.org/locations/
  - Prescribe to Prevent: Patient resources and videos demonstrating overdose recognition and response, including naloxone administration. • http://prescribetoprevent.org/video/
- Optionally (but highly encouraged), also educate and train at least one patient-authorized acquaintance (i.e., one who is likely to witness opioid overdoses such as a friend, family member, partner or carer).
- Instruct the patient to inspect the naloxone solution for particulate matter or discoloration, and check the expiration date. Avoid exposure of naloxone to prolonged temperature variations below 68° or above 77° F. For example, do not store naloxone in a vehicle subject to extreme high or low temperature changes.

Issue a maximum of one naloxone kit (2 doses / kit) or autoinjector carton (2 doses / carton) per prescription. Prescriptions may be marked for one refill.

Naloxone Dosage and Administration

Intramuscular (IM) Naloxone Kit	Intranasal (IN) Naloxone Kit	IM / Subcutaneous Naloxone Autoinjector
• Inject 0.4 mg in 1 ml IM (using vials), through clothing if necessary • May repeat dose in 3–5 minutes if no response • Dose may be repeated if apnea or hypopnea recurs	• Spray 1 mg in 1 ml in each nostril using atomizer device (each syringe contains 2 mg in 2 ml) • May repeat dose in 3–5 minutes if no response • Dose may be repeated if apnea or hypopnea recurs	• Administer 0.4 mg in 0.4 ml into the anterolateral aspect of the thigh, through clothing if necessary • May repeat doses every 2 to 3 minutes (each carton contains 2 doses)

Use requests to renew naloxone kit or autoinjector prescriptions as an opportunity to determine the circumstances (e.g., kit or autoinjector was used for overdose, lost, confiscated, expired, etc.) and base decisions to renew any prescriptions for opioids on the discussion with the patient and re-assessment of risk-benefit.

- Also use the discussion as an opportunity to engage the patient, re-assess risk-benefits, provide re-education about overdoses, review *Taking Opioids Responsibly* (as applicable), consider opioid risk mitigation strategies, and modify treatment plans.

To aid in national tracking of OEND program performance, providers should document opioid poisonings/overdoses in the medical record using the following ICD-10-CM code guidance:

- Begin with **DIAGNOSTIC CATEGORY T40**, followed by a
- **3 digit EXTERNAL CAUSE** code, followed by a
- **7th character DESCRIBING ENCOUNTER**

Because **DIAGNOSTIC CATEGORY T40** denotes "*Poisoning by, adverse effect of and underdosing of narcotics and psychodysleptics (hallucinogens)"* broadly, it is important to use one of the opioid-related **3 digit EXTERNAL CAUSE** codes to allow documentation of the specific agent involved (if known) and whether the event was unintentional, intentional, an assault, undetermined, or due to an adverse effect. The **7th character DESCRIBING ENCOUNTER** are suffix letters A or D (initial or subsequent encounter, respectively) or S (sequela; a complication or condition arising from the overdose event). See the Table below for opioid-related 3 digit external cause codes to be tracked nationally.

Table 1. Three digit external cause codes (added to T40 Diagnostic category) for documentation/tracking of opioid poisonings/overdoses

Poisoning by:	Accidental (unintentional)	Intentional self-harm	Assault	Undetermined	Adverse effect
Opium	T40.0X1	T40.0X2	T40.0X3	T40.0X4	T40.0X5
Heroin	T40.1X1	T40.1X2	T40.1X3	T40.1X4	N/A
Other opioids	T40.2X1	T40.2X2	T40.2X3	T40.2X4	T40.2X5
Methadone	T40.3X1	T40.3X2	T40.3X3	T40.3X4	T40.3X5
Other synthetic narcotics	T40.4X1	T40.4X2	T40.4X3	T40.4X4	T40.4X5
Unspecified narcotics	T40.601	T40.602	T40.603	T40.604	T40.605
Other narcotics	T40.691	T40.692	T40.693	T40.694	T40.695

Comparison of Kit and Autoinjector Routes of Administration

Topic	Intramuscular (IM) Naloxone	Intranasal (IN) Naloxone	IM / SC Naloxone Autoinjector
Onset	• 2–3 min	• 2–3 min	• Specific data not available
Time to "Response"†	• Mean 6–8 min[6,7]	• Similar[6] or longer by 2 min[7] than IM • Mean 4.2 ± 2.7 min; median 3 min[15] • Range 2–13 min[2,7,14]	• Mean 6–8 min[6,7] • Mean 9.6 ± 4.6 min (SC)[3]
Duration	• Not well documented; longer than IV, which has a duration of 30 min to 4 h • Dependent on amount, type and route of opioid	• Not well documented; see comments for IM naloxone	• Not well documented; see comments for IM naloxone
Advantages	• Formulation manufactured for this route • Seems to have similar responder rates vs. IV naloxone in prehospital settings[4] • Involves fewer steps to assemble • Simpler for some people (e.g., those familiar with using injections)	• Reduces risk of blood-borne virus transmission in a high-risk population • Reduces risk of needlestick injuries • Obviates need for needle disposal • Easy access to nares • May be preferred by people with aversion to needles or injections	• Pocket-size; convenient; portable • Shown to be relatively easy to use even without prior training in English-speaking individuals (adults took on average about 60 sec (range, 30–160 sec) to administer simulated injections. • Retractable needle may reduce accidental needle sticks and risk of blood-borne virus transmission in a high-risk population • The needle is not seen before, during

			or after the injection; this may be a desirable feature for persons who have an aversion to the sight of needles. • Discourages re-use of the device by injection drug users. • The auto-injector cannot be opened by hand and modified; opening it by using a tool is difficult and renders it nonfunctional. • Can be stored in a wider temperature range • The auto-injector case provides adequate protection from light
Disadvantages	• Risk of blood-borne virus transmission (e.g., HIV, HBC, HCV) • Risk of needlestick injuries • Risk of injury from improper injection technique • Proper use requires competence in techniques for extraction of drug from vial and injection • Requires adequate muscle mass	• May have lower bioavailability vs. IM route[5] • Similar[6] or slower[7] onset vs. IM route • Similar[6] or slightly lower[7] responder rates vs. IM naloxone • May be more likely to require supplemental doses of naloxone[6] • Not manufactured in a formulation for this route (the injectable form is aerosolized) • Nasal abnormalities (e.g., epistaxis, trauma, deformity, mucous) and prior intranasal drug use may reduce effectiveness[11] • Involves more steps to assemble	• If the voice instructions fail, persons with poor vision may have difficulty reading the label instructions because of the small font size • Restriction to IM or SC route of administration • Needle length in children less than 1 year old; the skin should be pinched to prevent the needle from contacting bone. If the needle strikes bone, the needle may be broken or damaged and delivery of drug may be obstructed. • Lack of field testing by Overdose Education and Naloxone Distribution (OEND) programs.
Other Considerations	• More common in U.S. naloxone programs[59] • Carpujects are a potentially less costly alternative to vials; however, anecdotal reports suggest that the carpujects are more difficult to assemble, prices fluctuate, and carpujects have not been field-tested.	• Off-label use; very low-quality evidence that IN and IV/IM are similar in clinical effects[8,9] • Associated with successful opioid overdose reversals using 1 mg/ml per naris (total 2 mg/2 ml)[10,11,12,13,14,] and 2 mg/ml (experimental).[15] • Extent of nasal absorption is dependent on mucosal surface area coverage, which is optimized by using an atomizer and limiting quantity to 1 ml per naris.[16]	• The 4-year battery life for the voice instructions exceeds the product expiration. • Whether training is required in non-English speaking individuals has not been evaluated; FDA required human factor testing in English speaking individuals..
Disposal of Used or Expired Product	• Biohazard sharps container	• Biohazard waste container	• Biohazard sharps container

† "Response" was defined in various ways (respiratory rate [RR] >10; increase in RR or Glasgow Coma Scale >6; return of spontaneous respiration; or "a significant improvement in consciousness") or not defined in the studies.

RECOMMENDATIONS FOR FACILITIES

Facilities should maintain a process to document the circumstances of naloxone dispensing, utilization and patient refusal of an offer for naloxone. Documentation should be done with the first prescription and upon each renewal.

Facilities may stock intramuscular or intranasal naloxone kits, both types of kits, intramuscular / subcutaneous autoinjectors, or all of these products. However, facilities should have a process to allow for individualized selection of the product and route of administration for naloxone.
See the Comparison of Kit and Autoinjector Routes of Administration section for advantages and disadvantages.

EVIDENCE-BASED CLASSIFICATION

Based on research to date on the effectiveness of OEND programs[13] and on risk factors for opioid-related overdose or suicide,[17–51,65] patients may be classified based on the strength and type of available evidence for the purpose of considering the provision of VA OEND. The VA OEND program recommends offering overdose education to all Veterans who are at increased risk for opioid overdose or who are prescribed or using opioids and request a naloxone kit. Provider discretion, patient requests and preferences, and perhaps regional overdose patterns[52] play roles in deciding which patients should be prescribed naloxone kits. Figure 1 summarizes the available evidence and serves as a guide for prioritization of patients for VA OEND.

Figure 1 Classification of OEND Candidates

Direct Association with Benefit	Indirect Association with Potential Benefit	Clinical Judgment of Potential Benefit
Risk criteria used in community health OEND programs associated with reduction in opioid overdose deaths*	Factors associated with an increased risk for fatal or nonfatal opioid overdose or any drug overdose death in U.S. Veterans. Some of these criteria have been used by an established OEND program without outcome data.	Common factors found in drug overdose deaths in nonveterans; factors associated with increased risk for nonfatal overdose or for respiratory depression from opioid therapy, and other clinical factors suggested by experts
• Heroin or other injection drug use • Substance use • Opioid or drug use disorder diagnosis • High likelihood of opioid overdose or witnessing an opioid overdose. High risk individuals have been targeted in the following settings: ○ Medication Assisted Treatment Program ○ Inpatient 'withdrawal management' (particularly individuals recently released from abstinence programs) ○ HIV education / prevention program ○ Syringe access program ○ Outpatient and residential SUD treatment programs ○ Community meetings / Support group programs for SUD ○ Emergency departments (recent medical care for opioid poisoning / overdose or intoxication) ○ Homeless shelters ○ Primary health care	Identified Patient Risk Factors • SUD diagnosis • PTSD or other MH diagnosis • Suspected or confirmed history of heroin or nonmedical opioid use • Male Veterans 30–59 years old • Any opioid prescription and known or suspected smoking, COPD, emphysema, asthma, sleep apnea, other respiratory system disease; renal or hepatic disease; alcohol use Identified Prescription Risk Factors • High-dose opioid prescription (50 to 100 mg or more MEDD) • Long-acting non-tramadol opioid • Methadone initiation in opioid-naïve patients • Opioid prescription with concomitant benzodiazepine use or concurrent antidepressant prescription Situational Risk Factors or Criteria • Loss of opioid tolerance and likely to restart opioids (e.g., recent release from jail or prison / post-incarceration re-entry programs) • Remoteness from or difficulty accessing [emergency] medical care • Voluntary patient request Settings Used to Target Those at Risk • Pain management clinics • Single room occupancy hotels [e.g., affordable housing for homeless people and people with mental illness or AIDs].	Identified Patient Risk Factors • Previous suicide attempt or on high-risk suicide list • Outpatient opioid prescription with the following: ○ Unstable renal or hepatic disease ○ Cardiac illness ○ HIV/AIDS ○ Age 65 years or older, cognitive impairment or debilitated condition ○ Voluntary caregiver request Identified Prescription Risk Factors • Home-based continuous intraspinal opioid infusion • Home-based patient-controlled opioid infusion • Opioid rotation to methadone • Opioid induction, upward titration or rotation (for SUD or pain) Situational Risk Factors • Fear of police arrest (reluctance to call 911) • Aberrant opioid use / misuse (e.g., early fills; extra doses; overlapping, multi-site fills).

Sources: 13,42–76
COPD, Chronic obstructive pulmonary disease; MEDD, Morphine-equivalent daily dose; MH, Mental health; SUD, Substance use disorder
*The examples of potential candidates for naloxone kits shown on page 2 were based on these risk criteria. Some of the criteria were modified on page 2 to make them VA-specific (e.g., homeless shelters was modified to Domiciliary care or community-based treatment for homeless Veterans. Those shown here reflect the criteria used by the Massachusetts OEND program.

RISK OF OPIOID OVERDOSE DEATHS IN VETERANS

A literature search found no studies providing mortality rates related to overdose of illicit opioids (e.g., heroin) in U.S. Veterans.

Available published estimates of the risk of fatal opioid-related overdoses in U.S. Veterans who were prescribed opioids are shown in Table 2:.

Table 2: Rates of Opioid-related Deaths in Veterans Prescribed Opioids

***Outcome* / Condition**	**Rate**
Opioid-related Accidents and Overdoses[77†]	*Proportion in 1-year of Follow-up (2005–2008), n/N (%)*
No MH diagnosis	1/4488 (0.02%)
MH Diagnosis without PTSD	6/3205 (0.19%)
PTSD with or without other MH diagnosis	29/7983 (0.36%)
Opioid Overdose Death[17§]	*Overall Proportion in 5-year Period (FY04–08), n/N (%)*
Opioid prescription	750/1,834,250 (0.04%)
Opioid Overdose Death[17§]	*Unadjusted Rate per 1000 Person-Months (FY04–08), (95% CI)*
Chronic noncancer pain, 50 to <100 mg MEDD	0.66 (0.53–0.82)
Chronic noncancer pain, ≥100 mg MEDD	1.24 (1.04–1.48)
Cancer diagnosis, 50 to <100 mg MEDD	0.49 (0.27–0.82)
Cancer diagnosis, ≥100 mg MEDD	0.98 (0.63–1.46)
Acute pain, 50 to <100 mg MEDD	1.13 (0.78–1.59)
Acute pain, ≥100 mg MEDD	1.82 (1.31–2.47)
SUD diagnosis, 50 to <100 mg MEDD	1.59 (1.05–2.31)
SUD diagnosis, ≥100 mg MEDD	2.97 (2.16–3.99)
Opioid Overdose Death[78]	*Rate Per 100,000 Person-years of All VHA Patients for Each Year (FY01 / FY09)*
Nonsynthetic opioids[‡]	4.2 / 7.2
Methadone	1.9 / 3.2
Synthetic / Semisynthetic opioids[††]	1.4 / 1.4
Age-adjusted Opioid Overdose Deaths by State[78]	*Rate Per 100,000 Person-years of All VHA Patients (FY01–09)*
Lowest rate: Mississippi	1.9
Highest rate: Utah	33.9

[†] Among Veterans who received at least 1 opioid prescription within 1 year of an index noncancer pain diagnosis

[§] Excluded patients in palliative/hospice care.

[‡] Examples of nonsynthetic opioids: codeine, morphine

[††] Examples of synthetic and semisynthetic opioids: fentanyl, meperidine, buprenorphine; , oxycodone, hydrocodone, oxymorphone, hydromorphone

Abbreviations: MEDD, maximum morphine-equivalent daily dose; MH, Mental health; PTSD, Posttraumatic stress disorder

In studies involving Veterans prescribed opioids, the diagnostic patient groups associated with higher risks of opioid overdose death were (1) those with a mental health diagnosis or PTSD with or without other mental health diagnosis (relative to no mental health diagnosis); and (2) those taking 100 mg or more of morphine equivalent daily doses and who had a substance use disorder (relative to those with chronic noncancer pain or cancer pain diagnosis).

A case-control study evaluated factors associated with serious toxicity or overdose in Veterans prescribed opioids (1 October 2010 to 30 September 2012).[53] The factors that were associated with significantly increased odds of the outcome of interest (life-threatening opioid-related respiratory or central nervous system depression or overdose) by a factor of 2 or more in the cases (N = 817) relative to the controls or references (N = 8,170) were opioid dependence (odds ratio [OR] 3.9; 95% CI: 2.6–5.8); 1 or more days of hospitalization in the preceding 6 months relative to zero days (all-cause health care utilization; 2.9; 2.3–3.6); moderate or severe liver disease (2.7; 1.1–6.7); hydromorphone (2.4; 1.2–4.7); skin ulcers (2.4; 1.5–3.8); metastatic solid tumor (2.3; 1.3–4.0); and pancreatitis (2.2; 1.1–4.5). Rheumatologic disease (0.3; 0.1–0.9) and tramadol (0.7; 0.5–1.0) were associated with significant reduction in the odds of serious toxicity ($p \leq 0.043$ for both ORs). The ORs for maximum prescribed daily morphine equivalent daily doses associated with serious toxicity or overdose relative to a reference of 1 to <20 mg were 1.5 (1.1–1.9) for 20 to <50 mg; 2.2 for 50 to <100 mg; and 4.1 (2.6–6.5) for ≥100 mg (all p-values ≤ 0.011).

Review of Overdose Education and Naloxone Distribution (OEND)

BACKGROUND

Naloxone is a safe and effective opioid antagonist that works predominantly at mu-opioid receptors and less so at kappa- and delta-opioid receptors. Its safety is due to its specificity; its only action is to reverse opioid mediated effects, which include respiratory depression, central nervous system depression and hypotension. Naloxone does not reverse the effects of alcohol, benzodiazepines or other central nervous system depressants. Naloxone is an undoubtedly highly effective intervention for reversing opioid overdoses and has been used for this purpose by emergency departments and emergency services personnel in the U.S. and abroad for decades.

Since 1996, community-based programs such as syringe exchange and other harm reduction programs for injection drug users began to offer naloxone and other opioid overdose educational services to drug users, their families and friends, health care providers, substance use disorder treatment programs and other service providers (e.g., homeless shelters). Overdose education and naloxone distribution (OEND) programs aim to ensure that individuals who are likely to require naloxone therapy are educated and trained about overdose and naloxone administration. Many OEND programs target people most likely to be present during an opioid overdose (e.g., family and peers), thereby improving chances of immediate resuscitative intervention and naloxone administration.

Other potential benefits of OEND programs include facilitating engagement of patients, empowering family and friends, and keeping individuals alive so they can enter addiction recovery.[54] OEND programs appear to have reduced utilization of emergency care for opioid overdoses.[55,56,57] With OEND programs, emergency medical services are reported to be involved in only 10% to 31% of overdoses, suggesting the potential for OEND to reduce the need or use of such resources for opioid overdoses.[12,57,58]

As observations emerged that OEND programs might prevent numerous opioid-related overdose deaths, the support for OEND programs grew in the U.S. and abroad. The World Health Organization recommends naloxone as an essential intervention to prevent overdose. According to a report by the Centers for Disease Control and Prevention, the Global Fund to Fight AIDS, Tuberculosis, and Malaria supports naloxone distribution to drug users.[59] The American Medical Association (AMA),[60] American Public Health Association (APHA)[61], and the U.K. Advisory Council on the Misuse of Drugs (ACMD)[54] support opioid overdose education and training and provision of naloxone to prevent opioid overdose, especially among high-risk populations such as illicit drug users. Moreover, in 2010, Scotland became the first country to implement a national naloxone program.[62] In response to public health concerns about opioid overdose, in 2013 the Substance Abuse and Mental Health Services Administration (SAMHSA) released an Opioid Overdose Prevention Toolkit.[63] This toolkit suggests that patients on long-term opioid therapy or who are at risk for overdose (e.g., completing abstinence programs) may benefit from education and access to naloxone kits.

The VA has had an increasing concern about the risk of opioid-related deaths among Veteran patients and endorses efforts to reduce overdose mortality. The success of OEND programs as a harm reduction strategy to reduce overdose mortality among high risk groups has prompted several VA facilities to develop and pilot OEND programs. Expecting that other facilities will follow suit, the VA Office of Mental Health Operations and Mental Health Services in collaboration with the Pharmacy Benefits Management Services (PBM) have prepared these recommendations for issuance of naloxone kits to support national implementation of OEND within the VA.

POTENTIAL BENEFITS AND HARMS OF OEND

Potential Benefits

Most of the current supporting data for OEND come from program evaluations of public health interventions. The majority of these programs target illicit drug users, their families and friends[64] and two programs target prescription pain medication users as well (e.g., Project Lazarus,[65] Operation OpioidSAFE—Fort Bragg). There are no published data on the effectiveness of OEND or implementation strategies from randomized trials to date; however, research is ongoing and there are a few randomized controlled trials that have been funded.

According to the results of a Harm Reduction Coalition survey, during 1996–2010, 48 community-based OEND programs (including 188 local programs) in the U.S. provided training and naloxone to 53,032 drug users, their families and friends, and service providers and received reports of 10,171 overdose reversals using naloxone.[59] Injectable naloxone was

dispensed by 42 (87.5%) of the 48 programs (63% of total vials); intranasal naloxone by 4 (8.3%) programs (33.1% of total vials); and both injectable and intranasal naloxone were dispensed by 4 (8.3%) programs (3.9% of total vials). The survey findings suggested that the OEND programs might have prevented numerous opioid-related overdose deaths.

The best available evidence of the benefits associated with OEND programs was published by Walley, et al.[13] In this comparative observational study, community public health OEND programs in 19 Massachusetts communities (2006–2009) issued intranasal naloxone to potential opioid overdose bystanders, including opioid users at risk for overdose, social service agency staff, family, and friends of opioid users. Of 327 rescue attempts made by 212 bystanders of the 2912 enrollees (potential overdose bystanders trained in OEND), information on naloxone use was available for 153 bystander overdose rescue attempts. Naloxone was successful in 98% of the reported cases (150 / 153). In the 3 unsuccessful naloxone rescue attempts, the person who overdosed survived after receiving emergency medical services care. With the extent of missing data (i.e., information was missing for 2700 enrollees [2912 minus 212]), the 150 reported cases of successful naloxone rescues represented 5.2% of the 2912 trained enrollees. The comparative analyses of the data used two models. The Absolute Model compared the rates of opioid-related deaths in terms of community 'density' of enrollment of OEND programs per 100,000 population using categories of 'No implementation' (reference value), 'Low implementation' (1–100 enrollments) and 'High implementation' (>100 enrollments). The Relative Model analyses used community-year strata relative to median cumulative implementation rates: 'No implementation' (reference value), 'Low implementation' (below the median) and 'High implementation' (above the median). Similar analyses were done for opioid overdose related acute care hospital utilization. Results are shown in Table 3.

Table 3 Evaluation of Associations Between OEND Implementation and Opioid Overdose Related Death and Acute Care Hospital Utilization

	Rate Ratio†	ARR (95% CI)	Rate Ratio†	ARR (95% CI)
Implementation Category	Death Rates		Acute Care Hospital Utilization	
Absolute Model				
Low: 1–100 enrollments§	0.93	0.73 (0.57–0.91)*	1.00	0.93 (0.80–1.08)
High: >100 enrollments§	0.82	0.54 (0.39–0.76)*	1.06	0.92 (0.75–1.13)
Relative Model				
Low: <median	0.85	0.71 (0.57–0.90)*	0.96	0.90 (0.76–1.07)
High: >median	1.00	0.78 (0.60–1.01)‡	1.10	1.00 (0.86–1.16)

* P < 0.01; † Reference was 'No Implementation'; ‡ P = 0.06; § Per 100,000 population. ARR, Adjusted rate ratio.

The results of this observational study provided low-quality evidence suggesting that OEND was associated with a 27% to 46% absolute reduction in opioid overdose fatalities (adjusted rate ratios) depending on the size of enrollments relative to no implementation. A causal relationship could not be established with the observational study design. The authors noted there was a 'dose-related' effect (by high or low implementation category) for death rates using the Absolute Model. This finding was inconsistently shown depending on the analytical model and the 95% confidence intervals for opioid overdose death rates overlapped, so one cannot definitely conclude there is a 'dose-related' effect. Naloxone reversals were based on unconfirmed self-reports; nonetheless, they are likely to have been underreported in this study, since their quantification was limited to only the overdose rescue attempts that were reported to the OEND programs.

POTENTIAL HARMS OF OEND

The risk of harms has not been adequately described in published studies of OEND programs. Potential harms to naloxone recipients in an OEND program can be primarily related to naloxone and technique- and injection-related accidents. Naloxone produces virtually no pharmacologic effects in patients not taking opioids, is not addictive, and is not associated with tolerance.

Precipitated Opioid Withdrawal. Naloxone can precipitate opioid withdrawal in a dose-related manner in persons with physical dependence to opioids. The higher the dose of naloxone, the longer and more severe the withdrawal syndrome will be. Withdrawal symptoms may start within minutes of a naloxone dose and may last about 2 hours. Naloxone administered intravenously may be titrated to minimize withdrawal symptoms by giving small doses every several minutes; titration is not recommended by the IM and IN routes of administration. The incidence of precipitated withdrawal in OEND programs has not been evaluated. One case series evaluated adverse events following out-of-hospital administration of naloxone (IM combined with IV up to a total dose of 2.4 mg) by paramedics in Oslo, Norway. Adverse events occurred in 45% of episodes, and 33% were related to opioid withdrawal (e.g., gastrointestinal disorders, aggressiveness, tachycardia, shivering, sweating and tremor).[66] Confusion (32%) may also have been related to withdrawal. Seizures (4%) were attributed to hypoxia by the authors, but seizures have also been associated with naloxone administered for reversal of lifethreatening opioid intoxication.[67]

Recurrence of Respiratory Depression. Opioids with long durations due to formulation design (e.g., extended-release tablets, capsules or patches) or inherently slow systemic clearance (e.g., buprenorphine, levorphanol and methadone) may outlast the duration of effects of naloxone. Naloxone has a half-life of 30 to 81 minutes (mean 64 ± 12 minutes). The duration of naloxone is dependent on the route of administration; being longer with IM than IV.[68] Duration of IN naloxone is not well described. The incidence of recurrent respiratory depression after bystander administration of naloxone is unknown; however, in the Massachusetts community-based OEND program experience, 52% of bystanders used 2 or more doses of naloxone.[13]

Pulmonary Edema. In postoperative patients treated with opioids for acute pain, high or rapidly administered doses of naloxone have been associated with acute pulmonary edema, hypertension and cardiac arrhythmia / arrest, presumably by inducing catecholamine release. There were many confounding factors in these cases, and a causal relationship with naloxone is unclear. Negative-pressure pulmonary edema (NPPE) has also been reported in postoperative patients given opioids for acute pain then naloxone to reverse respiratory depression. NPPE can occur if a person takes a deep breath when the glottis / upper airway is closed (which could occur after upper airway surgery for obstructive sleep apnea, for example). In these situations, providers need to be prepared to manage pulmonary edema and establish an airway before giving naloxone. Pulmonary edema has not been reported after layperson naloxone rescue but is still a potential concern.

Accidental Needlesticks and Transmission of Bloodborne Viruses. The IM route of administration may be associated with a risk of accidental needlesticks and transmission of HIV, HBV and HCV in a population at high risk of carrying or being infected with these viruses. The risk of accidental needlesticks as an injury and the risk of transmission of bloodborne viruses during layperson naloxone rescue attempts have not been evaluated.

Other Adverse Events. In one report describing the experience of the San Francisco Drug Overdose Prevention and Education (DOPE) project (in which naloxone was distributed to syringe exchange programs, re-entry programs, pain management clinics, methadone maintenance and buprenorphine treatment programs, and single room occupancy hotels), bystander rescuers reported other adverse events, including that the person became angry or was “dope sick” after naloxone reversal (36/399, 9%); was arrested (1/399, 0.2%); or was harassed by emergency medical services or police (11/399, 3%).[69]

Pain and Suffering from Inappropriate Use in Hospice / Palliative Care Patients. The signs and symptoms of life threatening opioid overdose overlaps with and may be mistaken for the common signs and symptoms of the dying process. A family member may erroneously administer naloxone to a Veteran approaching death, causing opioid reversal, withdrawal symptoms, pain and suffering. Family members of Veterans in hospice programs who receive OEND training should simultaneously receive education about the overlap in signs and symptoms with the dying process.

POTENTIAL BARRIERS TO OEND

Naloxone Supply Shortages. In the report by the Harm Reduction Coalition on community-based OEND programs, nearly half (43.7%) of the responding opioid overdose programs reported problems obtaining naloxone related to cost and the supply chain, and price increases of some formulations of naloxone appeared to restrict the program activities and the possibility of new programs.[64]

Concerns about Increased Opioid Use. One concern about making naloxone more readily available to opioid addicts is the potential unintentional consequence of encouraging increased opioid use because take-home naloxone may be perceived as a safety net.[70] The ACMD’s review of naloxone availability in the United Kingdom showed no evidence suggesting that naloxone provision encourages increased opioid use.[54] Another study showed similar results.[71] Two other studies have shown that drug use decreased with OEND intervention.[57,72]

Unwillingness to Carry Naloxone. In one study, participants often did not have the naloxone readily available for administration in a witnessed overdose because of the inconvenience or bulkiness of transporting the product and fear of being stigmatized for carrying injectables.[73] Concerns about bulkiness apply to the IN naloxone kit as well. A person’s own abstinence treatment goals may also be a barrier to carrying injection paraphernalia. In primarily injection drug user populations, possible repercussions by police or emergency medical service personnel have also been potential barriers. The word “overdose” may be associated with the stigmatization that the patient is irresponsible with opioid therapy. Some have suggested changing the word “overdose” to “safety” (i.e., Opioid Safety) when targeting patients prescribed opioids. Patients may fear that naloxone use will result in opioid discontinuation or dosage reduction.

Difficulty Assembling or Administering Naloxone. Some providers[74] and potential rescuers may find certain formulations of naloxone to be difficult to assemble or administer.

Medicolegal Concerns. Prescribers may be concerned that naloxone will most likely be administered to and by individuals other than the patient named on the prescription. Precedents counteracting these concerns are the provision of drugs that are expected to be administered by family members, such as epinephrine for treating anaphylaxis and glucagon injections for reversing severe hypoglycemia. Some states in the U.S. have enacted laws and regulations that

provide limited liability for prescribers in OEND programs. Some states have enacted Good Samaritan laws to protect bystanders from arrest or to encourage them to call emergency services and administer naloxone.

MODELS OF OEND

A number of models of OEND to decrease rates of fatal opioid overdose have been implemented successfully in non-VA settings. In general, OEND can be characterized by three models of distribution that have varying degrees of evidence: (1) Initial Public Health Model, (2) Expanded Public Health Model, and (3) Health Care Model.

The first model of OEND—the **Initial Public Health Model**—has the greatest amount of supporting evidence of effectiveness and cost-effectiveness. It has also been referred to as ("underground") Naloxone Prescription Programs (NPPs). The Initial Public Health Model involves naloxone distribution to high-risk individuals in the community (e.g., injection heroin users at needle exchanges). In the initial Chicago Recovery Alliance program, outreach workers directly contacted active injection drug users (IDUs) for naloxone distribution from vans, storefronts and designated cell phone or pager access sites.[75] A recent cost-effectiveness analysis modeled on naloxone distribution to 20% of heroin users suggests that it could prevent 6% (95% CI, 0.7% to 19.5%) of overdose deaths (1 for every 227 (95% CI, 71 to 716) kits distributed) and at a base case price of $25 per kit, is cost-effective, increasing costs by $53 and quality-adjusted life-years by 0.119 for an incremental cost-effective ratio (ICER) of $438. Even in a conservative model (e.g., where overdose was rarely witnessed and naloxone rarely used) the ICER was $14,000, well-below the typical cost-effective cut-off of $50,000[76]. Cost-effectiveness has not been examined in other populations.

The second model of OEND—the **Expanded Public Health Model**—expands distribution among high-risk populations to include potential bystanders (e.g., social service agency staff, family, friends of opioid users). The Harm Reduction Coalition's nationwide survey results suggested that OEND programs that distributed naloxone to persons who use drugs, their families and friends, and service providers might have saved a substantial number of lives.[59] As described previously, Walley, et al. (2013) evaluated this model in 19 communities in Massachusetts and found that communities that implemented OEND using IN naloxone had significantly reduced deaths related to opioid overdoses compared with those that did not implement OEND.[13] Compared with communities that had not implemented OEND, those that had implemented OEND had lower adjusted rate ratios for opioid overdose related deaths, 0.54 and 0.73, for high and low implementation categories, respectively (see Table 3). Walley, Doe-Simkins, et al. (2013) reported further on the feasibility of expanding OEND programs into methadone maintenance treatment programs, detoxification / withdrawal management programs, HIV prevention programs, and other settings such as community meetings, outpatient and residential addiction treatment programs, emergency departments and homeless shelters.[77]

The third model of OEND—the **Health Care Model**—involves distribution to patients by health care systems. Examples of these models include Scotland's national naloxone program and Fort Bragg's Operation OpioidSAFE (modeled on Project Lazarus[65]). Scotland established a national program in 2010 based on successful pilot programs in both urban and rural areas of Scotland. They have primarily been distributing to patients via harm reduction (needle exchange and outreach) and substance use disorder (SUD) treatment programs. Patient Group Direction allows qualified nurses or pharmacists to supply naloxone to anyone they identify as at risk of opioid overdose; notably, with consent, naloxone may also be given to family/friends of the at-risk patient. They are currently developing a general practice supply model and have conducted research that could inform VA implementation efforts. For instance, Scotland's pre-implementation assessment of knowledge, barriers, and enablers for naloxone distribution through general practice found that factors enabling naloxone distribution included appropriate training, evidence of effectiveness, and addition of the drug to the formulary[78]. OEND has also been provided through pharmacists practicing in community pharmacy settings and outpatient clinics.[79]

There is increasing interest in implementing OEND to patients prescribed opioids, but limited experience with this model of distribution. Fort Bragg's Operation OpioidSAFE and the San Francisco Department of Public Health have implemented programs targeting prescription opioid patients; however, there are no published data available at this time. Project Lazarus, upon which Operation OpioidSAFE was based, is a community-based overdose prevention program in rural North Carolina that uses a multifaceted approach to overdose prevention comprised of five components: (1) community activation and coalition building; (2) monitoring and surveillance data; (3) prevention of overdoses; (4) use of rescue medication for reversing overdoses by community members; and (5) evaluating project components. Major efforts include educating primary care providers in managing chronic pain and safe opioid prescribing (including naloxone distribution). Their take-home naloxone provision model involves physicians trained by Project Lazarus identifying "naloxone priority" patients based on 13 priority group criteria for overdose risk (e.g., recent opioid overdose; recent release from abstinence program; high dose opioid prescription [≥ 100 mg/day morphine equivalence]; and methadone prescriptions for opioid naïve patients). Patients who agree to participate in Project Lazarus watch a 20-minute DVD in the physician's office. The DVD covers topics such as patient responsibilities in pain management, recognizing and responding to an opioid overdose, and options for SUD treatment. Patients are prescribed a free naloxone kit. Because this approach is community-based and multi-faceted, it is difficult to generalize their findings to a health-care based model; however, preliminary unadjusted data suggest that the overdose death rate in Wilkes County dropped from 46.6 per 100,000 in 2009 to 29.0 per 100,000 in 2010.[65]

NALOXONE KIT CONTENTS

Naloxone kit contents have been selected based on the experience of other OEND programs (Table 4). Pre-assembled naloxone kits will contain materials needed for intramuscular or intranasal naloxone administration.

Table 4 Naloxone Kit Contents

Intramuscular Naloxone Kit	Intranasal Naloxone Kit
(2) Naloxone 0.4 mg/ml (1 ml) vials	(2) Naloxone 1 mg/ml (2 ml) prefilled needleless syringe
(2) Syringe, 3 ml with 25G 1-inch needle	(2) Mucosal Atomizer Device (MAD 300)
(2) Alcohol pads	(1) Laerdal face shield CPR barrier or equivalent
(1) Laerdal face shield CPR barrier or equivalent	(1) Pair of gloves
(1) Pair of gloves	(1) Overdose Rescue instructions
(1) Overdose Rescue instructions	(1) Opioid Safety brochure
(1) Opioid Safety brochure	(1) Zippered pouch
(1) Zippered pouch	

STAFF TRAINING AND RESOURCES

VA OEND SharePoint

- **The OEND National Support and Development Work Group develops provider training and patient and provider educational materials.**
- **Educational, informational and implementation resources are available to all VA staff via the OEND SharePoint. The link to this SharePoint is: https://vaww.portal2.va.gov/sites/mentalhealth/OEND/SitePages/Home.aspx**
- *Guide to Developing and Managing Overdose Prevention and Take-Home Naloxone Projects*[12] This comprehensive guide includes curricula for staff and patient training and educational materials. The curricula and materials have been posted on the VA OEND SharePoint.

SAMHSA OEND Resources

- **SAMHSA has created an Opioid Overdose Prevention toolkit with additional materials to facilitate implementation and education at: http://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/SMA13-4742**

Community OEND Programs

- **Existing community OEND programs can be located at: http://hopeandrecovery.org/locations/**

California Society of Addiction Medicine (CSAM) Naloxone Resources

- Multiple resources for naloxone recipients and their families, including videos on how to talk to patients about naloxone rescue, are available at: **http://www.csam-asam.org/naloxone-resources**

PATIENT AND BYSTANDER TRAINING

OEND training focuses on teaching patients who are likely to be bystanders at an overdose to recognize an opioid overdose, call emergency medical services (“911”), administer naloxone, perform the “ABCs” (Airway, Breathing and Circulation) of emergency response, and place the victim into the recovery position. In many cases, just administering naloxone will be enough to prevent a fatal overdose. The benefits of training bystanders have been evaluated in two studies that had inconsistent findings. In one study, those who received training were significantly better than those who received no training and were as skilled as medical experts in recognizing opioid overdose scenarios and the scenarios in which naloxone was indicated.[80] In the other study, there was no difference in rescue response behavior between the trained and untrained participants.[71] One of the intents of training is for the trainee to train his/her peers. In the Massachusetts OEND experience, the person who overdosed was most frequently a friend (69%), and less often a family member (16%), stranger (10%) or self (5%).[13]

Although naloxone can only be prescribed and dispensed to the patient under the care of the health care provider, training can be provided without necessarily dispensing a naloxone kit; anyone accompanying the patient and for whom the

patient has given consent can receive training, including opioid users (inpatients or outpatients), friends, partners, family members and carers.

According to the UK's ACMD report *Consideration of Naloxone* (May 2012)*, "*The NTA [National Treatment Agency] concluded that there is limited evidence that carers are the most appropriate people to receive naloxone training. They state that while training carers is beneficial in itself, training service users and providing overdose training and naloxone to as many people as possible may need to be considered to achieve a wider impact on overall fatal and non-fatal overdose rates. This includes service users who do not have a direct carer."[54]

Training individual clients in the community has been accomplished in as little as 3 minutes; however, typically 10 minutes is sufficient. Importantly, training should be tailored to meet the needs of the audience/patient.[7] Considerations for how to train patients will likely depend on treatment setting. Staff could be trained to provide 60-minute group training sessions, 3-10 minute individual training directly to patients, or in busy clinics such as primary care, training could be delivered in an alternative form (e.g., training video, handouts).

Updated Oct 2015 (ICD-10 information), June 2015 (amended refills) and May 2015 (added autoinjector). Original Prepared: June 2014. Contacts: Francine Goodman, PharmD, BCPS and Michael Chaffman, PharmD, BCPS, National PBM Clinical Pharmacy Program Managers

Acknowledgements: Elizabeth M. Oliva, PhD, prepared the OEND proposal document upon which substantial portions of these recommendations and review are based.

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